# Allergen immunotherapy for IgE-mediated food allergy

## a systematic review and meta-analysis

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REVIEW ARTICLE

# Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis

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allergen immunotherapy; food allergy; safety; desensitization; sustained unresponsiveness.

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## Abstract

**Background:** The European Academy of Allergy and Clinical Immunology (EAACI) is developing Guidelines for Allergen Immunotherapy (AIT) for IgE-mediated Food Allergy. To inform the development of clinical recommendations, we sought to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT in the management of food allergy.

**Methods:** We undertook a systematic review and meta-analysis that involved searching nine international electronic databases for randomized controlled trials (RCTs) and nonrandomized studies (NRS). Eligible studies were independently assessed by two reviewers against predefined eligibility criteria. The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and the Cochrane ACROBAT-NRS tool for quasi-RCTs. Random-effects meta-analyses were undertaken, with planned subgroup and sensitivity analyses.

[Correction added on 24 May 2017 after first online publication: The author names, Abstract section and Local Reactions Section were incorrect and have been corrected in this version.]

[The copyright line for this article was changed on November 22, 2017 after original online publication]

**Results:** We identified 1814 potentially relevant papers from which we selected 31 eligible studies, comprising of 25 RCTs and six NRS, studying a total of 1259 patients. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated sublingual immunotherapy, and one study evaluated epicutaneous immunotherapy. The majority of these studies were in children. Twenty-seven studies assessed desensitization, and eight studies investigated sustained unresponsiveness postdiscontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR) = 0.16, 95% CI 0.10, 0.26) and suggested, but did not confirm sustained unresponsiveness (RR = 0.29, 95% CI 0.08, 1.13). Only one study reported on disease-specific quality of life (QoL), which reported no comparative results between OIT and control group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses.

**Conclusions:** AIT may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. It is, however, associated with a modest increased risk in serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, long term effects, the impact on QoL and the cost-effectiveness of AIT.

Food allergy may result in considerable morbidity and, in some cases, mortality (1). Epidemiological studies have demonstrated that the prevalence and severity of food allergy may be increasing, particularly in children (2–8). Food allergies can be divided into IgE-mediated acute allergic reactions manifesting as urticaria, vomiting, wheezing and anaphylaxis, and non-IgE-mediated food allergy which results from delayed, cell-mediated reactions. This systemic review is focused on IgE-mediated reactions.

Food allergies can be associated with significant reduction in disease-specific quality of life (QoL) – both of individuals who suffer from food allergy and their family members (9, 10). At present, avoidance measures are the cornerstone of management (11). Difficulties in avoiding responsible food allergens can, however, result in accidental exposure and the risk of triggering potentially life-threatening anaphylaxis. Of concern is the increasing numbers of people being seen in emergency departments or who are hospitalized because of food-induced anaphylaxis (12, 13). Individuals with food allergy may therefore need to carry adrenaline (epinephrine) auto-injectors in order to self-manage anaphylaxis. This approach is, however, perceived as restrictive and still leaves patients at risk if accidental exposure occurs (2, 7, 8).

Allergen immunotherapy (AIT) has been used for over a century to treat those with food allergy (14). It involves repeated administration of gradually increasing doses of the antigens to which individuals are allergic in the hope of allowing safe exposure to the food(s) in question. Whilst AIT has become an established treatment regimen in relation to the management of, for example, pollen and insect venom allergy (15), it has yet to become established in the routine management of food allergy.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines for AIT, and this systematic review and meta-analysis is one of five interlinked assessments of the current evidence base in relation to evaluating AIT for the treatment of food allergy, allergic rhinoconjunctivitis, venom allergy, allergic asthma and allergy prevention, which will be used to inform development of clinical recommendations. The focus of this review, which builds on our previous related reviews (16, 17), is to assess the effectiveness, safety and cost-effectiveness of AIT in the management of IgE-mediated food allergy.

## Methods

Details of the methods employed in this review, including search terms and filters, databases searched, inclusion and exclusion criteria, data extraction and quality appraisal, have been previously reported (18). We therefore confine ourselves here to a synopsis of the methods employed.

### Search strategy

Nine international databases were searched for published material: Cochrane Library, which includes CENTRAL [Trials, Methods studies, Health Technology Assessments (HTA), Economic Evaluation database (EED)]; MEDLINE, EMBASE, ISI Web of Science, TRIP and CINAHL. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix S1: search strategies 1 and 2). Our database searches covered from inception to 31 March 2016. The bibliographies of all eligible studies were scrutinized to identify additional possible

studies. No language restrictions were imposed and where necessary manuscripts were translated into English.

### Inclusion criteria

*Patient characteristics*

We focused on studies conducted on children and adults of any age with a clinician-diagnosed IgE-mediated food allergy to milk, eggs, peanuts, tree nuts and other foods with confirmation of allergic status through positive skin prick tests, specific-IgE and/or food challenge tests.

*Interventions of interest and comparators*

This review focused on AIT for different allergens, that is milk, eggs, tree nuts, peanuts and other foods, administered through the following routes: oral (OIT), sublingual (SLIT) and epicutaneous (EPIT). We were interested in studies comparing food allergy AIT with placebo or routine care (i.e. adrenaline auto-injector with or without antihistamines) or no treatment.

*Outcomes*

Our primary outcomes of interest were as follows: (i) desensitization (i.e. the ability to safely consume foods containing the allergen in question whilst on AIT); (ii) sustained unresponsiveness (i.e. the ability to safely consume foods containing the allergen in question after discontinuing AIT) at food challenge; and (iii) changes in disease-specific QoL using a validated instrument. Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side effects (19, 20); health economic analysis from the perspective of the health system/payer as reported in studies.

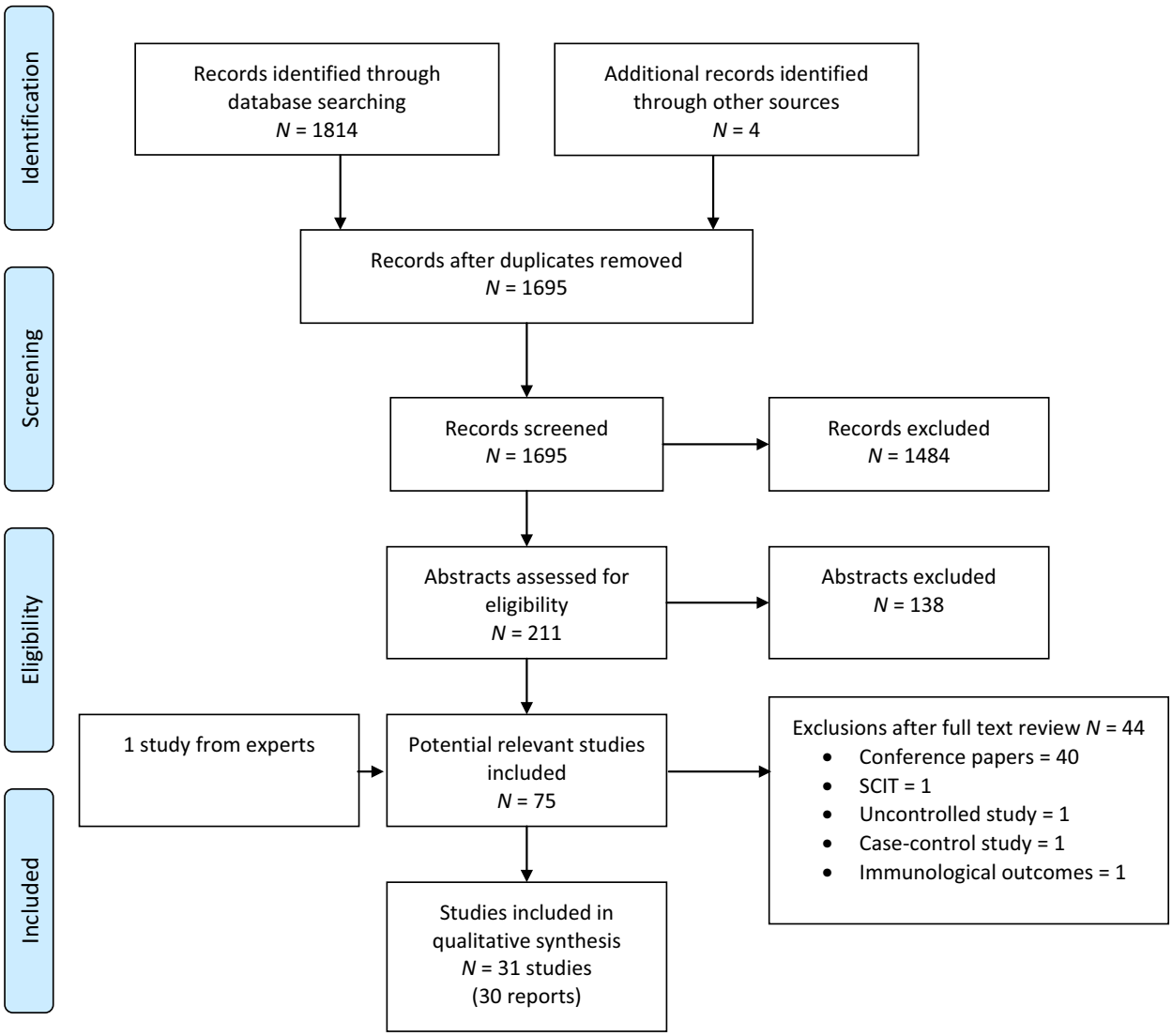


**Figure 1** PRISMA flow diagram.

**Table 1** Description of the included studies ($n$ = 31)

| | Food allergen (s) | | | | | | | | Route AIT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study (first author, year, country) | Cow's milk | Hen's egg | Peanut | Hazelnut | Peach | Apple | Fish | Other(s) | OIT | SLIT | EPIT |
| RCT ($n$ = 25) | | | | | | | | | | | |
| Anagnostou, 2014, UK | | | X | | | | | | X | | |
| Burks, 2012, USA | | X | | | | | | | X | | |
| Caminiti, 2009, Italy | X | | | | | | | | X | | |
| Caminiti, 2015; Italy | | X | | | | | | | X | | |
| Dello Iacono, 2013, Italy | | X | | | | | | | X | | |
| Dupont, 2010, France | X | | | | | | | | | | X |
| Enrique, 2005, Spain | | | | X | | | | | | X[†] | |
| Escudero, 2015, Spain | | X | | | | | | | X | | |
| Fernandez-Rivas, 2009, Spain | | | | | X | | | | | X[‡] | |
| Fleischer, 2012, USA | | | X | | | | | | | X | |
| Fuentes-Aparicio, 2013, Spain | | X | | | | | | | X | | |
| Kim, 2011, USA | | | X | | | | | | | X | |
| Lee, 2013, Korea | X | | | | | | | | X | | |
| Longo, 2008, Italy | X | | | | | | | | X | | |
| Martorell, 2011, Spain | X | | | | | | | | X | | |
| Meglio, 2013, Italy | | X | | | | | | | X | | |
| Morisset, 2007, France[‡‡] | X | X | | | | | | | X | | |
| Pajno, 2010, Italy | X | | | | | | | | X | | |
| Patriarca, 1998, Italy | X | X | | | | X | X | | X | | |
| Salmivesi, 2012, Finland | X | | | | | | | | X | | |
| Skripak, 2008, USA | X | | | | | | | | X | | |
| Staden, 2007, Germany | X | X | | | | | | | X | | |
| Tang, 2015, Australia | | | X | | | | | | X[††] | | |
| Varshney, 2011, USA | | | X | | | | | | X | | |
| CCT ($n$ = 6) | | | | | | | | | | | |
| García-Ara, 2013, Spain | X | | | | | | | | X | | |
| Martınez-Botas, 2015, Spain | X | | | | | | | | X | | |
| Mansouri, 2007, Iran | X | | | | | | | | X | | |
| Patriarca, 2003, Italy | X | X | X | | X | X | X | X[§] | X | | |
| Patriarca, 2007, Italy | X | X | | | | X | X | X[¶] | | X[‡] | |
| Syed, 2014, USA | | | X | | | | | | X | | |

AE, adverse event; AIT, allergen-specific immunotherapy; DR-QoL, disease-related quality of life; LR, local reaction; NR, not reported; OIT, oral immunotherapy; OFC, open food challenge; SLIT, sublingual immunotherapy; SR, systemic reaction.

[†]Sublingual-discharge technique.

[‡]Sublingual-swallow technique.

[§]Orange, corn, bean, lettuce.

[¶]Wheat, bean.

[††]AIT and probiotics.

[‡‡]One report that included two independent randomized controlled trials on cows' milk and hens' eggs.

*Study designs*

We were interested in RCTs investigating the role of OIT, SLIT or EPIT in children and adults with IgE-mediated food allergy. However, given the likelihood that we would find only a limited number of RCTs, we also searched for nonrandomized studies (NRS), these including non-randomized controlled clinical trials (CCTs), controlled before-and-after (CBA) studies and interrupted time series (ITS) analyses.

### Study selection

All references were uploaded into the systematic review software DistillerSR. Titles and abstracts of identified

| Comparator | | Evidence of allergy (mandatory inclusion criteria) | | | | | Clinical outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Occurred AEs / medication use | |
| Placebo | Routine care (food avoidance) | Clinical history | SPT &/ or sIgE | OFC | SBPCFC | DBPCFC | Desensitization | Sustained unresponsiveness | DR-QoL | SRs | LRs |
| | X | X | X | | | X | X | | X | X | X |
| X | | X | X | | | | X | X | | X | X |
| X | | X | X | | | X | X | | | X | X |
| X | | X | X | | | X | X | X | | X | X |
| | X | X | X | | | X | X | | | X | X |
| X | | X | X | X | | | X | | | X | X |
| X | | X | X | | | X | X | | | X | X |
| | X | X | X | | | X | | X | | X | X |
| X | | X | X | | | X | X | | | X | X |
| X | | | | | | | X | | | | |
| | X | X | X | X | | | X | X | | X | X |
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| | X | X | X | | | X | X | | | | X |
| | X | X | X | | X | | X | | | X | X |
| X | | X | X | | | X | X | | | X | X |
| | X | X | X | | | X | X | | | | X |
| X | | X | X | X | | | X | X | | X | X |
| X | | | X | | | X | X | | | X | X |
| | X | X | X | | | X | | X | | X | X |
| X | | X | X | | | X | X | X | | X | X |
| X | | X | X | | | | X | | | X | X |
| | X | X | X | X | | | X | | | X | X |
| | X | X | X | | | X | X | X | | X | X |
| | X | X | X | | | X | X | | | X | X |
| | X | X | X | | | X | X | | | X | X |
| | X | X | X | | | X | X | | | X | X |
| | X | X | X | | | X | | X | | NR | NR |

studies were checked and independently reviewed by two researchers (UN, SD). The full text of all potentially eligible studies was assessed for eligibility against the eligibility criteria (UN, SA). Any disagreements were resolved through discussion, with SD or AS arbitrating if agreement could not be reached.

### Quality assessment strategy

The quality of included RCTs was independently assessed by two reviewers (UN, SA) using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of Interventions (21). Critical appraisal of quasi-RCTs, CCTs

was undertaken using the Cochrane ACROBAT tool for NRS (22). An overall assessment of quality for each trial using these categories was arrived at through consensus discussion amongst reviewers.

### Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS).

Where possible and appropriate, data were synthesized using random-effects meta-analyses following the prespecified analysis plan. For the assessment of safety, as there were a number of studies with zero reported outcomes, to facilitate meta-analyses, we expressed safety data as the risk of not experiencing a local or systemic reaction. All analyses were undertaken using the software Comprehensive Meta-Analysis (version 3).

### Sensitivity, subgroup analyses and assessment for publication bias

Sensitivity analyses were undertaken by focusing on results from double-blind RCTs. Subgroup analyses were undertaken to compare:

- Diagnosis of food allergy was confirmed by double-blind, placebo-controlled, food challenge (DBPCFC) *vs* without DBPCFC.
- Route of administration: OIT *vs* SLIT *vs* EPIT.
- Children (0–17 years) *vs* adults (≥18 years).
- Type of AIT protocol: conventional *vs* rush.
- Allergens used for AIT.

Where possible, publication bias was assessed through the creation of funnel plots in Comprehensive Meta-Analysis (version 3).

### Registration and reporting of this systematic review

This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) with registration number: CRD42016039384.

## Results

Our searches identified 1814 potentially relevant papers, from which we identified 31 trials that satisfied our inclusion criteria studying a total of 1259 patients (Fig. 1: PRISMA flow diagram). There were 25 RCTs (23–46) and six NRS', all of which were CCTs (47–52). Twenty-five of these trials investigated OIT (23–27, 30, 33, 35–50, 52), one epicutaneous immunotherapy (EPIT) (28) and the remaining five investigated SLIT (29, 31, 32, 34, 51). One report included two independent RCTs on cow's milk (CMA) and hen's egg (HEA) (39). Sixteen studies focused on CMA (25, 35–37, 39–44, 47–51), 11 on HEA (24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51), seven on peanut (23, 32, 34, 45, 46, 50, 52), one hazelnut (29), two peach (31, 50), three apple (41, 50, 51), three fish (41, 50, 51) and two other studies focused on a variety of food allergens including orange, corn, bean, lettuce (50), wheat and bean (51) (see Table 1 and Appendix S2: Table S1). The trials were undertaken in Italy ($n = 9$), Spain ($n = 7$), the USA ($n = 6$), France ($n = 3$), Australia ($n = 1$), Finland ($n = 1$), Germany ($n = 1$), Iran ($n = 1$), Korea ($n = 1$) and the UK ($n = 1$).

### Quality assessment

Quality assessment of these studies revealed that eight of the RCTs were judged to be at low risk of bias (24, 26, 32, 34, 36, 40, 45, 46); a further five RCTs were judged as at unclear risk of bias (28, 31, 33, 37, 43), and the remaining 12 RCTs (23, 25, 27, 29, 30, 35, 38, 39, 41, 42, 44) were judged to be at high risk of bias (see Appendix S3: Table S2). The six CCTs (47–52) were all judged to be at moderate risk of bias (see Appendix S4: Table S3).

### Primary outcomes

*Desensitization*

Desensitization was assessed in 18 OIT RCTs (23–27, 33, 35–43, 45, 46) and five OIT CCTs (47–51). There were also four SLIT RCTs (29, 31, 32, 34) and one SLIT CCT (51) that assessed desensitization. The efficacy of AIT was compared with placebo in 12 studies, eight of which used OIT (24–26, 42, 43, 45, 46) and four of SLIT (29, 31, 32, 34); the other 17 studies, all of OIT, employed routine care (i.e. food avoidance/strict elimination diet as the comparator) (27, 30, 33, 35–39, 41, 44, 47–52).

Meta-analysis was possible with data from 27 trials investigating a total of 1171 subjects; this revealed a substantial benefit with respect to desensitization: relative risk (RR) = 0.16, 95% CI 0.10, 0.26; see Fig. 2A (23–27, 29–41, 43, 44, 46–52).

*Sensitivity analyses*

Sensitivity analysis of the 21 RCTs, excluding the six CCTs, also demonstrated a substantial benefit: RR = 0.21, 95% CI 0.13, 0.34; see Fig. 2B (23–27, 29–41, 43, 44, 46). A further sensitivity analysis excluding all trials judged to be at high risk of bias confirmed this substantial benefit: RR = 0.15, 95% CI 0.09, 0.25; see Fig. 2C (24, 26, 31–34, 36, 37, 40, 43, 46–52). A further sensitivity analysis excluding all trials (whether OIT or SLIT) judged to be at high risk of bias demonstrated a substantial average risk reduction (RR OIT = 0.17, 95% CI 0.11, 0.26) (24, 26, 33, 36, 37, 40, 43, 46–50) and (RR SLIT = 0.31, 95% CI 0.10, 0.98) (31, 32, 34) (see Appendix S5: Figs S1 and S2).

A final sensitivity analysis focusing on studies in which desensitization was confirmed by DBPCFC after OIT or SLIT also revealed substantial benefits (RR 0.15, 95% CI 0.09, 0.27; see Appendix S5: Fig. S3) (23, 25–27, 29–31, 35–41, 43, 44, 47–52).

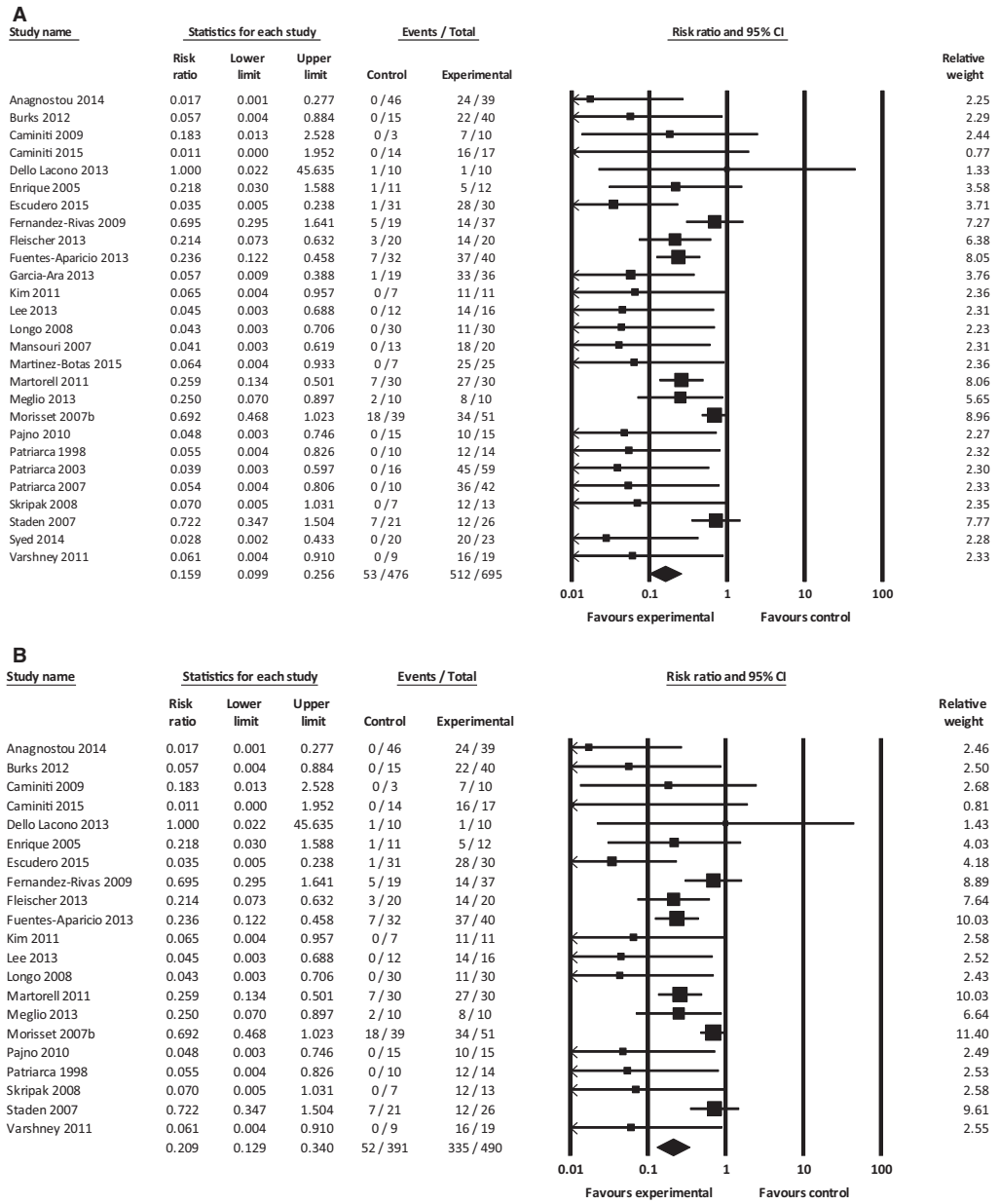


**Figure 2** (a) Risk ratios (RR) of desensitization following oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) *vs* controls (random-effects model). 2a: Heterogeneity: $\tau^2 = 0.617$; $\chi^2 = 62.845$, df = 26 ($P < 0.0001$); $I^2 = 59\%$; Test for overall effect: $Z = -7.582$ ($P < 0.0001$). 2b: Heterogeneity: $\tau^2 = 0.498$; $\chi^2 = 47.608$, df = 20 ($P < 0.0001$); $I^2 = 58\%$; Test for overall effect: $Z = -6.318$ ($P < 0.0001$). 2c: Heterogeneity: $\tau^2 = 0.262$; $\chi^2 = 23.078$, df = 16 ($P < 0.112$); $I^2 = 31\%$; Test for overall effect: $Z = -7.406$ ($P < 0.0001$).

*Subgroup analyses*

- Subgroup analysis based on the route of administration of AIT (OIT *vs* SLIT) revealed that both OIT (RR = 0.14, 95% CI 0.08, 0.24; see Fig. 3) (23–27, 30, 33, 35–41, 43, 44, 46–50, 52) and SLIT were effective (RR = 0.26, 95% CI 0.10, 0.64; see Fig. 4) (29, 31, 32, 34, 51).
- A subgroup analysis based on the age of the population studied (children aged up to 18 years old, adults ≥18 years old and mixed population that included subjects 0–55 years old) revealed a substantial average risk reduction only for children and mixed populations, but not for adults (RR, children's studies = 0.16, 95% CI 0.09, 0.27) (23–27, 30, 32–41, 43, 44, 46–49). (RR, adults = 0.56, 95% CI 0.23, 1.36) (29, 31) (RR, mixed population = 0.04, 95% CI 0.01, 0.19) (50–52) (see Appendix S5: Figs S4–S6).

C

| Study name | Risk ratio | Lower limit | Upper limit | Control | Experimental | Relative weight |
|---|---|---|---|---|---|---|
| Burks 2012 | 0.057 | 0.004 | 0.884 | 0 / 15 | 22 / 40 | 2.95 |
| Caminiti 2015 | 0.011 | 0.000 | 1.952 | 0 / 14 | 16 / 17 | 0.89 |
| Fernandez-Rivas 2009 | 0.695 | 0.295 | 1.641 | 5 / 19 | 14 / 37 | 14.43 |
| Fleischer 2013 | 0.214 | 0.073 | 0.632 | 3 / 20 | 14 / 20 | 11.55 |
| Fuentes-Aparicio 2013 | 0.236 | 0.122 | 0.458 | 7 / 32 | 37 / 40 | 17.43 |
| Garcia-Ara 2013 | 0.057 | 0.009 | 0.388 | 1 / 19 | 33 / 36 | 5.40 |
| Kim 2011 | 0.065 | 0.004 | 0.957 | 0 / 7 | 11 / 11 | 3.06 |
| Longo 2008 | 0.043 | 0.003 | 0.706 | 0 / 30 | 11 / 30 | 2.87 |
| Mansouri 2007 | 0.041 | 0.003 | 0.619 | 0 / 13 | 18 / 20 | 2.98 |
| Martinez-Botas 2015 | 0.064 | 0.004 | 0.933 | 0 / 7 | 25 / 25 | 3.06 |
| Martorell 2011 | 0.259 | 0.134 | 0.501 | 7 / 30 | 27 / 30 | 17.45 |
| Pajno 2010 | 0.048 | 0.003 | 0.746 | 0 / 15 | 10 / 15 | 2.93 |
| Patriarca 2003 | 0.039 | 0.003 | 0.597 | 0 / 16 | 45 / 59 | 2.96 |
| Patriarca 2007 | 0.054 | 0.004 | 0.806 | 0 / 10 | 36 / 42 | 3.01 |
| Skripak 2008 | 0.070 | 0.005 | 1.031 | 0 / 7 | 12 / 13 | 3.05 |
| Syed 2014 | 0.028 | 0.002 | 0.433 | 0 / 20 | 20 / 23 | 2.95 |
| Varshney 2011 | 0.061 | 0.004 | 0.910 | 0 / 9 | 16 / 19 | 3.01 |
| | 0.150 | 0.091 | 0.248 | 23 / 283 | 367 / 477 | |

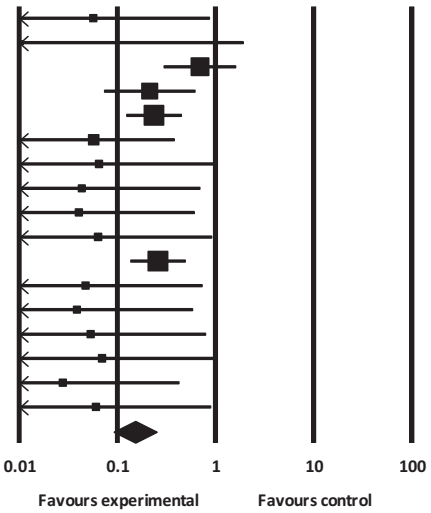


**Figure 2** Continued.

- Subgroup analysis based on the type of AIT protocol (conventional *vs* rush) also showed a substantial average risk reduction for both methods (RR, conventional protocol = 0.12, 95% CI 0.07, 0.21) (23–27, 30, 32–35, 38, 40, 43, 44, 46, 47, 49–52) (RR, rush = 0.33, 95% CI 0.16, 0.65) (29, 31, 36, 37, 39, 41, 48) (see Appendix S5: Figs S7 and S8).
- Subgroup analyses of types of allergen demonstrated that in 13 trials investigating CMA, 11 HEA and four peanut allergy OIT/SLIT substantially reduced the risk of desensitization to CMA, HEA and peanut allergy (RR CM = 0.12, 95% CI 0.06, 0.25) (25, 35–37, 39–41, 43, 44, 47–51) and (RR HE = 0.22, 95% CI 0.11, 0.45) (24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51) and (RR peanut = 0.11, 95% CI 0.04, 0.31) (23, 32, 34, 46) (see Appendix S5: Figs S9–S11). A sensitivity analysis of the 17 OIT and four SLIT RCTs found a substantial average risk reduction (RR OIT = 0.18, 95% CI 0.10, 0.32) (23–27, 30, 33, 35–41, 43, 44, 46) and (RR SLIT = 0.31, 95% CI 0.13, 0.76) (29, 31, 32, 34) (see Appendix S5: Figs S12 and S13).

The Funnel plot revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Fig. 5).

*Sustained unresponsiveness post-discontinuation of AIT*

There were seven OIT RCTs (24, 26, 30, 33, 42, 44, 45) and one OIT CCT (52) that investigated the longer-term effects of AIT between two weeks and 36 months after discontinuation of AIT (see Table 1 and Appendix S2: Table S1). Meta-analysis suggested, but did not confirm the benefits of OIT (RR = 0.29, 95% CI 0.08, 1.13) (24, 26, 30, 44) (see Fig. 6).

The Funnel plot also revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Fig. 7).

*Disease-specific quality of life*

Only one OIT RCT reported disease-specific QoL of patients and their families (23). This study used a validated questionnaire for parents, the Food Allergy Quality of Life Questionnaire Parent Form (FAQLQ-PF); however, no comparative results between OIT and the control group were reported at the end of the first phase of the study. Results are reported for the end of the second phase of the study at which time the control group had also received OIT.

## Secondary outcomes

*Safety*

*Systemic reactions*. Data on the occurrence of systemic adverse reactions during AIT were available from 25 trials (23–27, 29–31, 33, 35, 36, 39, 40, 42–51) (Table 1). However, there were different formats of reporting systemic reactions between trials, and we were therefore only able to pool data from seven studies (26, 29, 31, 35, 40, 46, 49). Meta-analyses of *not* experiencing a systemic reaction were higher in those receiving control: RR = 1.09, 95% CI 1.00, 1.19) (see Fig. 8) (26, 29, 31, 35, 40, 46, 49).

Subgroup analysis demonstrated that the risk of experiencing a systemic reaction was higher in those receiving OIT (RR of *not* experiencing a reaction in controls = 1.16, 95% CI 1.03, 1.30) (26, 35, 40, 46, 49). In contrast, data from two SLIT studies showed no difference between arms (RR of *not* experiencing a reaction in controls = 0.98, 95% CI 0.85, 1.14) (29, 31) (see Appendix S5: Figs S14 and S15).

Sensitivity analysis excluding all trials judged to be at high risk of bias after OIT or SLIT demonstrated either a borderline difference (RR of *not* experiencing a reaction in controls = 1.10, 95% CI 0.99, 1.23) (26, 31, 40, 46, 49) or a

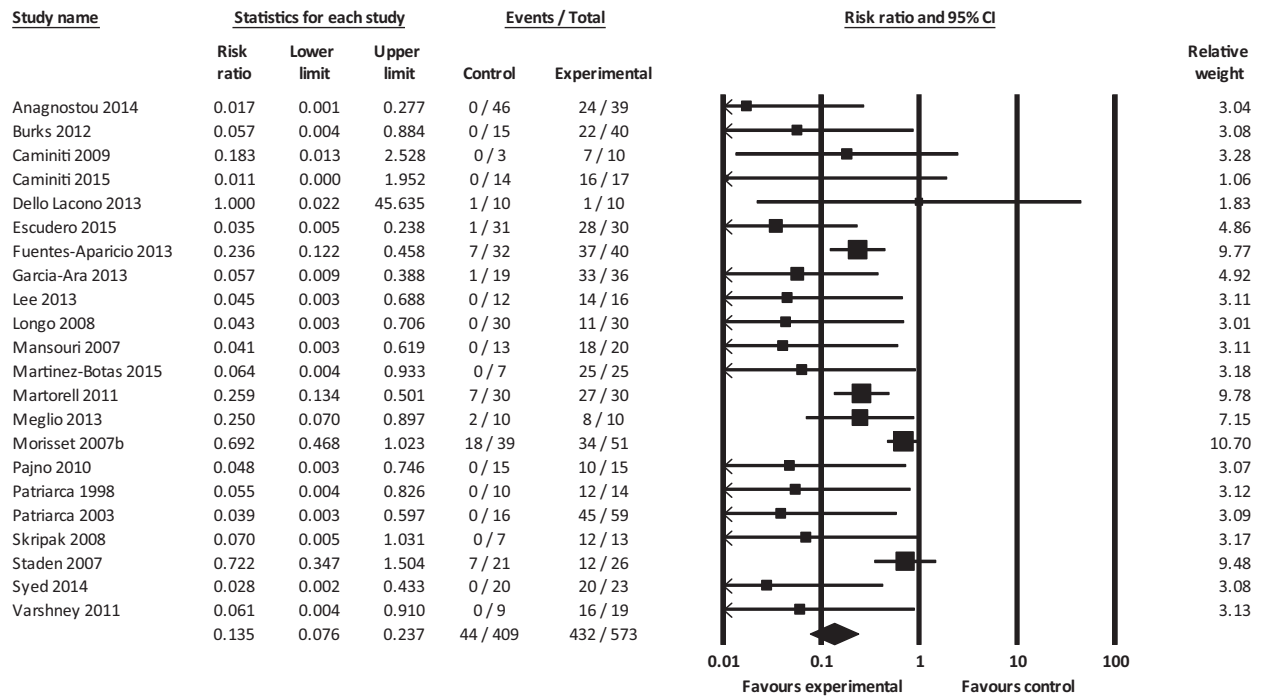


**Figure 3** Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in OIT v. controls (random-effects model). Heterogeneity: $\tau^2 = 0.735$; $\chi^2 = 56.047$, df = 21 ($P < 0.0001$); $I^2 = 62\%$; Test for overall effect: $Z = -6.967$ ($P < 0.0001$).

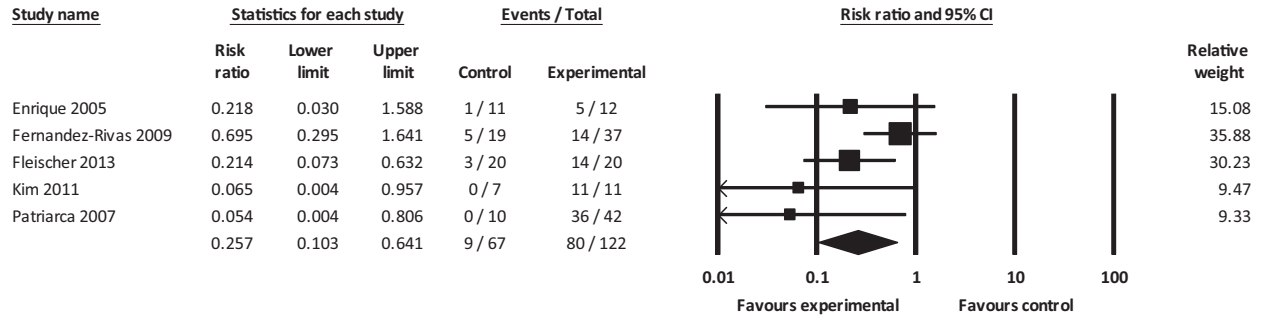


**Figure 4** Risk ratios (RR) of desensitization as assessed by double-blind, placebo-controlled food challenge in SLIT *vs* controls (random-effects model). Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 6.80$, df = 4 ($P < 0.147$); $I^2 = 41\%$; Test for overall effect: $Z = 2.91$ ($P < 0.004$).

significant difference in the rate of systemic reactions between the two arms after OIT (RR of *not* experiencing a reaction in controls = 1.17, 95% CI 1.03, 1.33) (26, 40, 46, 49) (see Appendix S5: Figs S16 and S17).

A subgroup analysis of CMA trials found that the risk of experiencing a systemic reaction was higher in the AIT arm (RR of *not* experiencing a reaction in controls = 1.19, 95% CI 1.03, 1.37) (35, 40, 49) (see Appendix S5: Fig. S18). Subgroup analysis of systemic reactions during OIT from five children's studies to cow's milk, egg or peanut showed a significant difference between the two arms; however, the pooled data from the two studies with adult populations using SLIT for peach or hazelnut allergy found no clear evidence of a difference in systemic reactions between the treatment arms and the control arms (RR of *not* experiencing a reaction in controls, children = 1.16, 95% CI 1.03, 1.30) (26, 35, 40, 46, 49) and (RR of *not* experiencing a reaction in controls, adult = 0.98, 95% CI 0.85, 1.14) (29, 31). The lack of a significant effect in adults may reflect a lack of precision (as the point estimate suggests benefit), which in turn is a function of the paucity of large trials in adult populations (see Appendix S5: Figs S19 and S20).

*Local reactions*

Data on occurrence of local adverse reactions during AIT (minor oropharyngeal/gastrointestinal/ perioral rash) were available from 28 trials (23–31, 33, 35–51) (see Table 1).

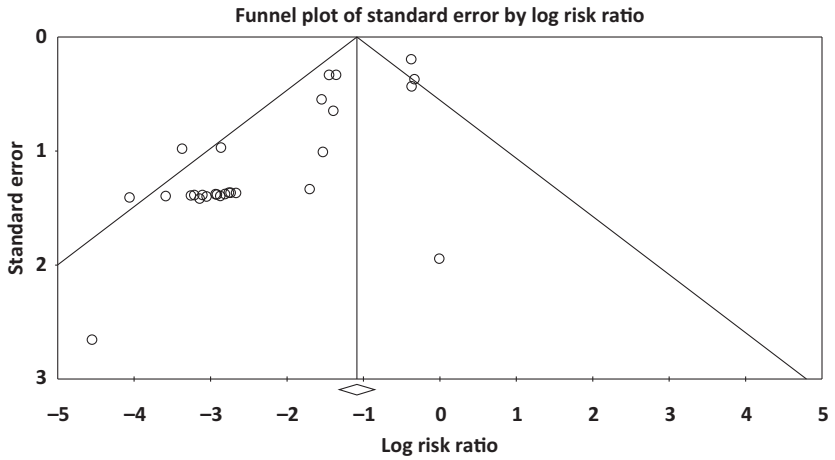


**Figure 5** Funnel plot showing: risk ratios (RR) of persisting food allergy after OIT or SLIT.

| Study name | Statistics for each study | | | Events / Total | | Risk ratio and 95% CI | Relative weight |
|---|---|---|---|---|---|---|---|
| | Risk ratio | Lower limit | Upper limit | Control | Experimental | | |
| Burks 2012 | 0.111 | 0.007 | 1.781 | 0 / 15 | 11 / 40 | | 15.56 |
| Caminiti 2015 | 0.243 | 0.032 | 1.844 | 1 / 14 | 5 / 17 | | 22.42 |
| Escudero 2015 | 0.088 | 0.012 | 0.640 | 1 / 31 | 11 / 30 | | 22.90 |
| Staden 2007 | 0.963 | 0.431 | 2.150 | 7 / 21 | 9 / 26 | | 39.12 |
| | 0.292 | 0.076 | 1.126 | 9 / 81 | 36 / 113 | | |

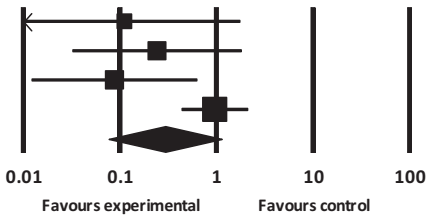


**Figure 6** Risk ratios (RR) of sustained unresponsiveness as assessed by double-blind, placebo-controlled food challenge in OIT v. controls (random-effects model). Heterogeneity: $\tau^2 = 1.043$; $\chi^2 = 7.044$, df = 3 ($P < 0.071$); $I^2 = 57\%$; Test for overall effect: $Z = -1.788$ ($P < 0.074$).

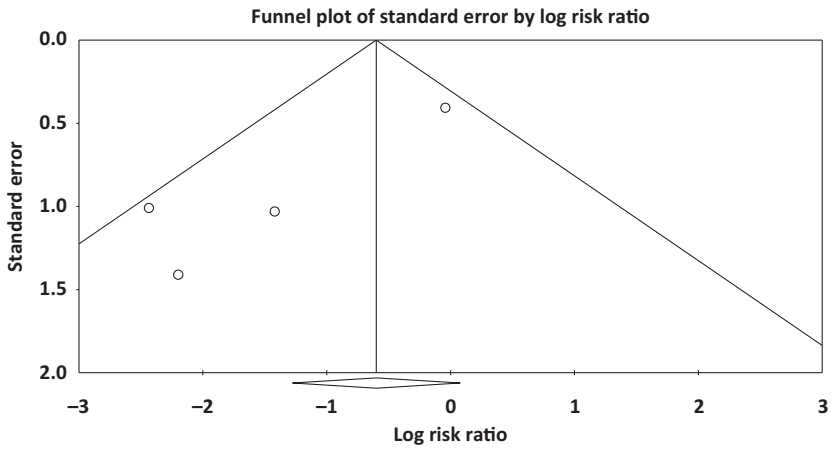


**Figure 7** Funnel plot showing: risk ratios (RR) of persisting food allergy after OIT or SLIT (only RCTs).

However, there were different formats of reporting reactions between trials, and we were therefore only able to pool data from nine studies. Meta-analyses of local reactions obtained from these nine trials demonstrated that AIT was associated with an increased risk of local reactions (RR of *not* experiencing a reaction in controls 2.12, 95% CI 1.50, 3.0) (24, 26, 28, 35, 37–40, 49) (see Fig. 9).

Subgroup analysis of local adverse events demonstrated higher risk of reactions in those receiving OIT (RR of *not* experiencing a reaction in controls = 2.14, 95% CI 1.47,

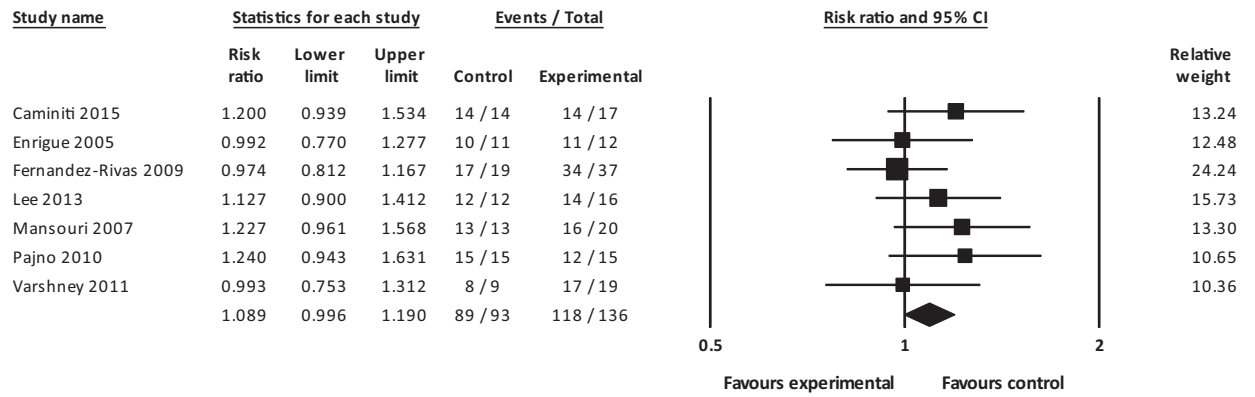


**Figure 8** Safety data – absence of systemic reactions during OIT or SLIT for food allergy. RR, risk ratio (random-effects model). Heterogeneity: $\tau^2 = 0.0001$; $\chi^2 = 4.87$, df = 6 ($P < 0.56$); $I^2 = 0\%$; Test for overall effect: $Z = 1.86$ ($P < 0.06$).

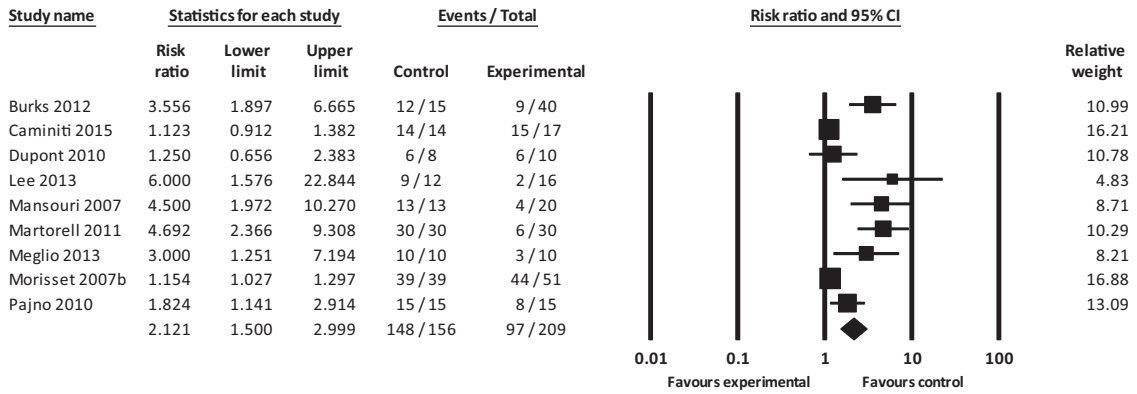


**Figure 9** Safety data – absence of local reactions during OIT or EPIT for food allergy. RR, risk ratio (random-effects model). Heterogeneity: $\tau^2 = 0.182$; $\chi^2 = 48.412$, df = 8 ($P < 0.0001$); $I^2 = 83\%$; Test for overall effect: $Z = 4.253$ ($P < 0.0001$).

3.12) (24, 26, 37–40, 49) (see Appendix S5: Fig. S21). A further sensitivity analysis excluding all trials judged to be at high risk of bias also showed an increased risk of local reactions in the treatment arms compared with the control arms (RR of *not* experiencing a reaction in controls = 2.58, 95% CI 1.43, 3.02) (24, 26, 37, 40, 49) (see Appendix S5: Fig. S22). Local reactions during OIT from only RCTs subgroup analysis demonstrated higher risk of local reactions in the AIT group (RR of *not* experiencing a reaction in controls = 2.08, 95% CI 1.43, 3.02) (24, 26, 35, 37–40) (see Appendix S5: Fig. S23). Another subgroup analysis of local reactions during OIT for CMA from either RCTs and CCTs or only RCTs also demonstrated increased risk of having local reactions in the AIT group (from RCTs and CCTs, RR of *not* experiencing a reaction in controls = 3.49, 95% CI 1.89, 6.43) and (35, 37, 39, 40, 49) (from RCTs, RR of *not* experiencing a reaction in controls = 3.29, 95% CI 1.50, 7.23) (35, 37, 39, 40) (see Appendix S5: Figs S24 and S25). Local reactions during OIT for HEA also found an increased risk of local reactions in the AIT arm (RR of *not* experiencing a reaction in controls = 1.55, 95% CI 1.09, 2.22) (24, 26, 38, 39) (see Appendix S5: Fig. S26).

The effect of the AIT protocol (conventional *vs* rush) on the occurrence of local reactions during the treatment was available only from OIT trials. Both, conventional and rush AIT protocols demonstrated an increased risk of local reactions in the treatment arm compared with the controls (RR of *not* experiencing a reaction in controls, conventional = 2.58, 95% CI 1.46, 4.55) (24, 26, 35, 38, 40, 49) (RR of *not* experiencing a reaction in controls, rush = 2.23, 95% CI 0.57, 8.80) (37, 39) (see Appendix S5: Figs S27 and S28).

*Health economic analysis*

None of the studies reported data on cost-effectiveness.

## Discussion

### Summary of main findings

This systematic review and meta-analysis has found evidence that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. This evidence comes mainly from studies

in children, and it is therefore still unclear if AIT is effective for adults. Pooling of the safety data demonstrated an increased risk of local and systemic reactions with AIT. No fatalities were reported during AIT. Only one study assessed QoL (23), which reported no comparative results between OIT and the control group. We found no data investigating the cost-effectiveness of AIT in patients with food allergy.

### Strengths and limitations of this work

We believe that this systematic review is the most robust investigation undertaken to date to support the use of AIT in children and adults with food allergy (53–60). A key strength of our systematic review was the comprehensiveness of the searches. We carefully identified and scrutinized the characteristics of all possible terms, including MeSH, EMTREE and free keywords for different types of food allergy and AIT. In addition, we encompassed all available bodies of evidence from all randomized and NRS, with a range of planned subgroup and sensitivity analyses.

The main limitations of this systematic review stem from the heterogeneity of included populations, interventions, outcomes, diversity of AIT protocols and treatment modalities, and definition of outcomes (e.g. adverse reactions). Due to the heterogeneity of studies, the meta-analyses need to be interpreted with caution. In an attempt to account for this heterogeneity, we undertook random-effects meta-analyses which produce more conservative assessments of benefits than would have been obtained using fixed-effects meta-analyses. That said, this is an area that will warrant further exploration of the possible sources of heterogeneity in follow-on work. We were also limited by the lack of data on long-term adverse outcomes (e.g. eosinophilic esophagitis) and lack of data on cost-effectiveness. Studies which were published after our cut-off date 31st March 2016 are not included in this review which may have provided additional evidence to support the effectiveness and safety of OIT (61).

## Conclusions

We found that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT, but was associated with an increased risk of local and systemic adverse events. Future trials need in particular to investigate the effectiveness of AIT in adults, understand the impact of AIT on disease-specific QoL of patients and family members, and establish the cost-effectiveness of AIT for food allergy.

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## Author contributions

Aziz Sheikh conceived this review. This study was drafted by Ulugbek Nurmatov, Sangeeta Dhami and Stefania Arasi. It was revised following critical review initially by Aziz Sheikh and then by all the co-authors. This study is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

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## Conflict of interests

Ulugbek Nurmatov, no conflict of interests; Sangeeta Dhami reports grants from EAACI to carry out the review; Stefania Arasi reports other from Evidence-Based Health Care Ltd during the conduct of the study; Giovanni Battista Pajno reports grants from Stallergenes during the conduct of the study; Montserrat Fernandez-Rivas reports grants from European Union, grants from Instituto de Salud Carlos Ill, Ministerio de Ciencia, Espaha, grants from Ministerio de Economia, Espaha, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, personal fees from ALK Abello, Merck, GSK, nonfinancial support from EAACI, personal fees and nonfinancial support from Fundaci6n SEAIC, other from Hospital Clinico San Carlos and Universidad Complutense de Madrid, outside the submitted work; in addition, Fernandez Rivas has a patent PT0042/2013 issued; Antonella Muraro reports personal fees from Novartis, personal fees from Meda Mylan, outside the submitted work; Graham Roberts has a patent use of sublingual immunotherapy to prevent the development of allergy in at risk infants, issued and his University has received payments for activities he has undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck; Cezmi Akdis reports grants from Actellion, personal fees from Aventis, personal fees from Stallergenes, grants and personal fees from Allergopharma, personal fees from Circassia, grants from Novartis, grants from Christine Kuhne Center for Allergy Research and Education, outside the submitted work; Alvaro has nothing to disclose; Kirsten Beyer reports grants from DBV, grants and personal fees from Aimmune, outside the submitted work; Carsten Bindslev-Jensen reports grants from Anergis, grants from AImmune, grants from HAL Allergy, outside the submitted work; Wesley Burks reports grants from Food Allergy & Anaphylaxis Network, grants from National Institutes of Health, grants from Wallace Research Foundation, during the conduct of the study; personal fees from FARE, personal fees from NIH AITC Review Panel, personal fees from NIH HAI Study Section, personal fees from World Allergy Organization, personal fees from Aimmune Therapeutics, Inc., personal fees from Epiva Biosciences, Inc.,

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Search strategy.
**Appendix S2.** Detailed characteristics of included studies.
**Appendix S3.** Risk of bias assessment of RCTs.
**Appendix S4.** Risk of bias assessment of CCTs.
**Appendix S5.** Additional forest plots.

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